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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,436	03/27/2001	Remi Delansorne	01056	5099

23338 7590 04/19/2007

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EXAMINER	
DESAI, ANAND U	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/787,436	DELANSORNE ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79,82,84-92,95 and 97-99* is/are pending in the application.

4a) Of the above claim(s) *85,86 and 88-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79,82,84,87,92,95 and 97-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 23, 2007 has been entered.

Election/Restrictions

2. The claims 85, 86, and 88-91 were previously withdrawn in the Final office action mailed July 5, 2006 (see paragraph 3 of office action mailed July 5, 2006). Claims 85, 86, and 88-91 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons: The claims are drawn to distinct methods of using the pharmaceutical composition that comprises a LH-RH analogue in combination with an α-cyclodextrin derivative. The distinct methods have different end effects, such as treating infertility, functioning as a contraceptive, or treating benign or malignant tumors.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 85, 86, and 88-91 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found

allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

4. Claims 79, 82, 84, 87, 92, 95, 97, 98, and 99 are currently under examination.

Specification

5. The disclosure is objected to because of the following informalities:

6. There is a typographical error when identifying amino acid sequences throughout the specification. See for example page 2, line 15, identifier written as "SEQ ID N° :". Reference to the sequence should use the identifier, "SEQ ID NO:". Applicant is referred to 37 CFR 1.821(2) (d). Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Appropriate correction is required.

Claim Objections

7. Claims 79, 84, 92, 95, and 99 are objected to because of the following informalities:

8. In claims 79 and 92, there is a typographical error when identifying amino acid sequences. The identifier is written as "SEQ ID N° :". Reference to the sequence should use the identifier, "SEQ ID NO:". Applicant is referred to 37 CFR 1.821(2) (d). Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

9. There is a space missing between "3,6", when describing hexakis (2, 3, 6-tri-O-methyl)-α-cyclodextrin in claim 79.

10. There is a typographical error in the recitation of the 2nd to last Markush member of the α-cyclodextrin derivatives in claim 79. There is an inadvertent comma between carboxymethylated and α-cyclodextrin. Suggest removing the comma.

11. In claim 84, there is an inadvertent space between the dash and α-cyclodextrin. Suggest hexakis (2, 3, 6-tri-O-methyl)-α-cyclodextrin.

12. Claim 95 has a typographical error. There is a period missing after the number 95.

13. In claim 99, although permethylated α-cyclodextrin is hexakis (2, 3, 6-tri-O-methyl)-α-cyclodextrin, it is confusing to write permethylated α-cyclodextrin instead of hexakis (2, 3, 6-tri-O-methyl)-α-cyclodextrin, because hexakis (2, 3, 6-tri-O-methyl)-α-cyclodextrin is recited in claim 79 as the Markush member. Suggest identifying permethylated α-cyclodextrin as hexakis (2, 3, 6-tri-O-methyl)-α-cyclodextrin in claim 99.

14. Claim 99 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 97. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim (see item 12 directly above, and page 12, line 9 of the specification). See MPEP § 706.03(k).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 79, 84, 87, 92, 97, 98, and 99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17. In claims 79, and 92, the claims recites the limitation "the α-cyclodextrin derivative" at the end of the claim describing the Markush group, but the preamble recites α-cyclodextrin as the element in the composition. There is insufficient antecedent basis for this limitation in the claim. Suggest, reciting the α-cyclodextrin in the preamble as the α-cyclodextrin derivative. The pharmaceutical composition is interpreted to be a LH-RH peptide analogue in combination with an α-cyclodextrin derivative rather than α-cyclodextrin as recited in the preamble.

18. In claims 79, and 92, it is unclear how A1, A3, and A5 are variables? The amino acid at position 1, 3, and 5 are not variable. Claims 84, 87, 97, 98, and 99 are rejected for depending on rejected claims 79 and 92.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claim 87 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of prostate cancer or benign prostatic hypertrophy, does not reasonably provide enablement for the prevention of prostate cancer or benign prostatic hypertrophy. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are rejected because of undue experimentation to practice the claimed method of preventing prostate cancer or benign prostatic hypertrophy.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

1) The nature of the invention: claim 87 is directed to a method to prevent prostate cancer or benign prostatic hypertrophy.

3) The predictability or unpredictability of the art: & 6) The quantity of experimentation necessary: & 7.) The state of the prior art: the prior art has shown a large quantity of experimentation is often necessary to overcome the unpredictable nature of cancer progression. The prior art has shown that all patients with metastatic prostate cancer will finally end in hormonal independent disease (mean: 24 months). Mean survival in patients with bone metastasis is 23-37 months (see Konstantinos, particularly page 803, 1st indented paragraph on left hand column). Consequently, there would be a large quantity of experimentation necessary to determine what pharmaceutical compositions are capable of preventing prostate cancer.

4) The amount of direction or guidance presented: & 5) The presence or absence of working examples: the specification is devoid of any examples that demonstrate the prevention of prostate cancer or benign prostatic hypertrophy upon administration of the pharmaceutical composition being claimed.

How would one of skill in the art use the method if it is unknown what pharmaceutical composition can prevent prostate cancer or benign prostatic hypertrophy?

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of the Wands factors, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 79, 82, 84, 87, 92, 95, 97, 98, and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirai et al. (U.S. 4,659,696) in view of Kurihara et al. (U.S. 5,051,402) and Kano et al. (Journal of Inclusion Phenomena and Molecular Recognition in Chemistry 22: 285-298 (1995)).

Hirai et al. teaches an LH-RH analog which is a polypeptide having the formula pGlu-His-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-NHC_2H_5 (or leuprorelin) and 5 g of α-cyclodextrin (see col. 21, line 13-26). This peptide analog fits the formula of I defined in claims 79, 82, 92, and 95. Various cyclodextrins are taught, including tri-O-methylcyclodextrin (see column 4, lines 23-38). "Absorption enhancer" in claim 98 is being interpreted as any excipient or pharmaceutical carrier that would increase the stability of the peptide. Thus, the excipient or

pharmaceutical carriers used by Hirai et al. would meet this limitation. Hirai et al. does not disclose leuprorelin with the particular α-cyclodextrin derivatives.

Claim 92 recites limitations that refer to the intended use of the pharmaceutical formulation. Where it is possible that structural differences exist between the formulation of Hirai et al. and that of the present invention, there is nothing recited in the claims that distinguishes the present invention from the prior art.

The present method claims are directed to a method of orally administering an LH-RH analog with α-cyclodextrin derivative. Whereas *Hirai et al.,* teach the composition of the claims, non-oral administration routes are taught as the preferred method of administration. Thus, *Hirai et al.* does not expressly teach a method of oral administration, but only allows an inference that a method was employed with reduced success. However, the teachings of Kurihara et al. teach that peptides for oral administration are made up as capsules that may contain α-cyclodextrin derivatives. Kurihara et al. employs α-cyclodextrin derivatives for the oral administration of peptides, which is the problem that the present invention seeks to resolve (see col. 4, lines 17-60, and claims 1, 10, and 11). Kano et al. describes an added benefit to using α-cyclodextrin derivatives, because of a more flexible cavity for the inclusion of guests in α-cyclodextrin derivative, hexakis (2, 3, 6-tri-O-methyl)-α-cyclodextrin. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the LH-RH peptides of *Hirai et al.* with alpha-cyclodextrin derivatives for the purposes of oral administration. A person of ordinary skill in the art would have been motivated to use the formulation for administration, as capsules comprising alpha-cyclodextrin derivatives have been used for the oral administration of peptides with some success. Thus, the claimed invention was

within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Conclusion

24. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on (517) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

April 12, 2007

Anand Desai